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(54) ENHANCED SKIN PENETRATION SYSTEM FOR IMPROVED TOPICAL DELIVERY OF DRUGS

System mit erhöhender Hautpenetration für verbesserte topische Verabreichung von Arzneimitteln

SYSTEME AMELIORE DE PENETRATION DE LA PEAU UTILISE POUR L'ADMINISTRATION LOCALE DE MEDICAMENTS

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(56) References cited:
EP-A- 0 150 933
EP-A- 0 165 770
EP-A- 0 261 865
EP-A- 0 319 964
EP-A- 0 395 282
WO-A-87/06595
US-A- 5 009 969

- **DATABASE WPIL Section Ch, Week 9016, 12 March 1990 Derwent Publications Ltd., London, GB; Class A09, AN 90-120588**
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Description

The present invention relates to compositions for th topical administration of drugs, especially such compositions having enhanced penetration of the drug through the skin.

Because of the accessibility and large area of the skin, it has long been considered a promising route for the administration of drugs, whether dermal, regional, or systemic effects are desired.

The advantages of the topical route of drug administration include: avoidance of the risks and inconvenience of parenteral treatment; avoidance of the variable absorption and metabolism associated with oral treatment; continuity of drug administration, permitting use of pharmacologically active agents with short biological half-lives; potential reduction of gastrointestinal irritation in systemic administration; and treatment of curtaneous manifestations of diseases usually treated systemically.

However, the impermeability of skin is well-known, serving as a barrier to ingress of pathogens and toxic chemicals, and egress of physiologic fluids. This impermeability is the result of normal physiologic changes in developing skin. A typical cell in the epidermis is formed in the basal layer. It typically takes approximately thirty days for a cell to migrate from the basal layer of the epidermis to sloughing off and discarding at the outer layers of the stratum corneum. As the cell migrates outward from the basal layer, it progressively keratinizes until it is relatively impermeable. The result is the stratum corneum, an extremely thin surface layer (10 microns) with substantial barrier properties. The cell envelopes of the cells in the stratum corneum tend to be mainly polar lipids, such as ceramides, sterols, and fatty acids while the cytoplasm of stratum corneum cells remains polar and aqueous. Despite the close packing of the cells, some 15% of the stratum corneum is intercellular and, generally, lipid based. It is generally recognized that over the very short term, penetration occurs through the hair follicles and the sebaceous apparatus; long-term penetration occurs across cells (non-polar route). Poor penetration of many drugs across the epidermal lipid barrier has, until now, frustrated attempts to deliver clinically significant doses of many drugs by the topical route.

One route of internal delivery of drugs is by transdermal administration. Transdermal administration of drugs can be used in many instances to achieve therapeutic levels of the drugs in the systemic circulatory system, as well as for more localized internal dosing of drugs. Where such therapeutic levels of drugs can be achieved by transdermal administration, several potential advantages exist over other routes of administration. Sustained systemic delivery of drug controlled at therapeutic but below toxic levels over long periods of time with a single continuous application is often an advantag of transdermal drug administration. Pot ntial contamination of internal tissues with undesired foreign substances or microbes, often associated with parenteral administration of drugs, is avoided with transdermal drug administration. Oral administration of many drugs is undesirable or unfeasible because the drug decomposes in the harsh environment of the gastrointestinal tract, lacks sufficient absorption from the gastrointestinal tract, or causes gastrointestinal upset or tissue damage in the gastrointestinal tract. First-pass metabolism of orally administered drugs can increase the dosage required to achieve therapeutic levels and thereby increase undesirable side effects either from the primary drug or the metabolites. Maintenance of uniform, optimal systemic levels of drugs for long periods of time is often difficult through oral administration. Such problems can often be reduced or avoided by transdermal drug administration.

Despite the substantial potential advantages for transdermal administration of drugs, relatively few drugs are so administered. The skin is a formidable barrier to the passage of most drugs. It is often necessary to provide a composition containing a skin penetration enhancing vehicle in order to provide sufficient transdermal penetration of the drug to achieve therapeutic levels of the drug at the target internal tissue. A number of skin penetration enhancing vehicles for drugs have been disclosed, including those in the following references: US-A-3,536,816 issued to Kellner on October 27, 1970; US-A-4,006,218 issued to Sipos on February 1, 1977; US-A-4,124,720 issued to Wenmaekers on November 7, 1978; US-A-4,126,681 issued to Reller on November 21, 1978; US-A-4,299,826 issued to Luedders on November 10, 1981; US-A-4,305,936 issued to Klein on December 15, 1981; US-A-4,309,414 issued to Inagi, Muramatsu & Nagai on January 5, 1982; US-A-4,338,306 issued to Kitao & Nishimura on July 6, 1982; US-A-4,442,090 issued to Kakeya, Kitao & Nishimura on April 10, 1984; US-A-4,485,033 issued to Kitao & Nishimura on November 27, 1984; US-A-4,537,776 issued to Cooper on August 27, 1985; US-A-4,552,872 issued to Cooper, Loomans & Fawzi on November 12, 1985; US-A-4,557,934 issued to Cooper on December 10, 1985; US-A-4,573,995 issued to Chen, Chun & Enscore on March 4, 1986; US-A-4,626,539 issued to Aungst & DiLuocio on December 2, 1986; US-A-4,637,930 issued to Konno, Kawata, Aruga, Sonobe & Mitomi issued January 20, 1987; US-A-4,695,465 issued to Kigasawa, Ohtani, Tanaka & Hayashida on September 22, 1987; EP-A-0,043,738 of The Procter & Gamble Company in the names of Wickett, Cooper & Loomans, published on June 13 1982; EP-A-0,095,813 of The Procter & Gamble Company in the name of Cooper, published December 7, 1983; PCT International Patent Application No. WO 87/03490 of Key Pharmaceuticals, Inc. in the names of Bodor and Loftson, published on June 18, 1987; Washitake, M., T. Anmo, I. Tanaka, T. Arita & M. Nakano, "Percutaneous Absorption of Drugs from Oily Vehicles", Journal of Pharmaceutical Sciences, Vol. 64, No. 3 (March, 1975), pp. 397-

401; Shahi, V., & J. L. Zatz, "Effect of Formulation Factors on Penetration of Hydrocortisone through Mouse Skin", Journal of Pharmaceutical Sciences, Vol. 67, No. 6 (June, 1978), pp. 789-792; Cooper, E.R., "Increased Skin Permeability for Lipophilic Molecules", Journal of Pharmaceutical Sciences, Vol. 73, No. 8 (August, 1984), pp. 1153-1156; Aungst, B.J., N. J. Rogers & E. Shefter, "Enhancement of Naloxone Penetration through Human Skin In Vitro Using Fatty Acids, Fatty Alcohols, Surfactants, Sulfoxides and Amides", International Journal of Pharmaceutics, Vol. 33 (1986), pp. 225-234; Green, P.G., & J. Hadgraft, "Facilitated Transfer of Cationic Drugs Across a Lipoidal Membrane by Oleic Acid and Lauric Acid", International Journal of Pharmaceutics, Vol. 37 (July, 1987), pp. 251-255. EP-A-0,395,282 relates to aqueous acidic solutions which are thickened by cationic polymers formed from a water-soluble cationic ethyleneically unsaturated monomer or blend of monomers that includes a polyethyleneically unsaturated crosslinking agent. However there is no mention in this document of the incorporation of such polymers into topical pharmaceutical compositions having enhanced penetration through the skin.

It is an object of the present invention to provide novel compositions for enhancing the in penetration of drugs.

It is a further object of the present invention to provide such compositions which provide sufficient skin penetration enhancement to achieve therapeutic levels of the drugs in target internal tissues. ,

It is a further object of the present invention to provide such compositions with low dermal irritation, especially in compositions requiring a low pH.

It is a still further object of the present invention to provide such compositions having good stability and good cosmetics.

According to the present invention there is provided a topical pharmaceutical composition having enhanced penetration through the skin characterized in that it comprises:

(a) a safe and effective amount of a pharmaceutical active selected from anti-acne drugs, non-steroidal anti inflammatory drugs, steroidal anti-inflammatory drugs, sunless tanning agents, sunscreen agents, wound healing agents, skin bleaching or lightening agents, antihistaminic drugs, antitussive drugs, antipruritic drugs, anticholinergic drugs, anti-emetic and antinauseant drugs, anorexic drugs, central stimulant drugs, antiarrhythmic drugs, β-adrenergic blocker drugs, cardiotonic drugs, antihypertensive drugs, diuretic drugs, vasodilator drugs, vasoconstrictor drugs, anti-ulcer drugs, anesthetic drugs, antidepressant drugs, tranquilizer and sedative drugs, antipsychotic drugs, antimicrobial drugs, antineoplastic drugs, antimalarial drugs, muscle relaxant drugs, antispamadic drugs, antidiarrheal drugs and bone-active drugs and mixtures thereof;

(b) from 0.1% to 10.0% of a high molecular weight crosslinked cationic polymer of the formula: $(A)_l(B)_m(C)_n$ wherein (A) is a dialkylaminoalkyl acrylate monomer or its quaternary ammonium or acid addition salt, (B) is a dialkylaminoalkyl methacrylate monomer or its quaternary ammonium or acid addition salt, (C) is a monomer having one carbon-carbon double bond, l is an integer of 0 or greater, m is an integer of 1 or greater, and n is an integer of 0 or greater, wherein said polymer contains a crosslinking agent.

In further embodiments the crosslinked cationic polymer is of the formula wherein (C) is acrylamide.

In further embodiments the crosslinked cationic polymer is of the formula wherein (C) is acrylamide and l is zero.

In yet further embodiments the crosslinked cationic polymer is a homopolymer wherein both l and n are zero.

All concentrations and ratios herein are by weight of total composition and all measurements are at 25°C, unless otherwise specified.

The present invention involves compositions comprising certain specific cationic polymers which may be applied topically to the skin and which result in improved transdermal penetration of the drugs through the skin. These compositions also have a high solvent tolerance, i.e., high level of solvents such as alcohol and other water-soluble components which may be necessary to solubilize the active can be included in the compositions.

Drug Active

The compositions of the present invention comprise a safe and effective amount of a drug active. The phrase "safe and effective amount", as used herein, means an amount of a drug high enough to significantly positively modify the condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgement. A safe and effective amount of the drug will vary with the specific drug, the ability of the composition to penetrate the drug through the skin, the amount of composition to be applied, the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, and like factors.

The drug compounds present in the compositions of the present invention preferably comprise from about 0.1% to about 20% by weight of the compositions, more preferably from about 0.1% to about 10%, and most preferably from about 0.1% to about 5%. Mixtures of drug actives may also be used.

Useful drug actives in the compositions of the present invention include anti-acne drugs. Anti-acne drugs preferred for use in the present invention include

the keratolytics such as salicylic acid, sulfur, lactic acid, glycolic, pyruvic acid, urea, resorcinol, and N-acetylcysteine; retinoids such as retinoic acid and its derivatives (e.g., cis and trans); antibiotics and antimicrobials such as benzoyl peroxide, octopirox, erythromycin, zinc, tetracyclin, triclosan, azelaic acid and its derivatives, phenoxy ethanol and phenoxy proponol, ethylacetate, clindamycin and meclocycline; sebostats such as flavinoids; alpha and beta hydroxy acids; and bile salts such as scymnol sulfate and its derivatives, deoxycholate, and cholate. Preferred for use herein is salicylic acid.

Useful drug actives in the compositions of the present invention include non-steroidal anti-inflammatory drugs (NSAIDS). The NSAIDS can be selected from the following categories: propionic acid derivatives; acetic acid derivatives; fenamic acid derivatives; biphenylcarboxylic acid derivatives; and oxicams. All of these NSAIDS are fully described in the US-A-4,985,459 to Sunshine et al., issued January 15, 1991. Most preferred are the propionic NSAIDS including but not limited to aspirin, acetaminophen, ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic acid, fluprofen and bucloxic acid. Also useful are the steroidal anti-inflammatory drugs including hydrocortisone and the like.

Useful drug actives in the compositions of the present invention include antihistaminic drugs. Antihistaminic drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of chlorpheniramine, triprolidine, diphenhydramine, doxylamine, pyrilamine, phenindamine, promethazine, cyproheptadine, azatadine, clemastine, carbinoxamine, tripelennamine, terfenadine, dexchlorpheniramine, brompheniramine, chlorcyclizine, diphenylpyraline, pheniramine and phenyltoloxamine, and mixtures thereof.

Useful drug actives in the compositions of the present invention include antitussive drugs. Antitussive drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of dextromethorphan, codeine, caramiphen and carbetapentane.

Useful drug actives in the compositions of the present invention include antipruritic drugs. Antipruritic drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of methdilizine and trimeprazine.

Useful drug actives in the compositions of the present invention include anticholinergic drugs. Anticholinergic drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of scopolamine, atropine, homatropine, levodopa, dicyclomine, hyoscyamine, procyclidine, trihexyphenidyl and ethopropazine.

Useful drug actives in the compositions of the present invention include anti-emetic and antinauseant drugs. Anti-emetic and antinauseant drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of cyclizine, meclizine, chlorpromazine, buclizine, metoclopramide, prochlorperazine and trimethobenzamide.

Useful drug actives in the compositions of the present invention include anorexic drugs. Anorexic drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of benzphetamine, phentermine, chlorphentermine, fenfluramine, diethylpropion and phendimetrazine.

Useful drug actives in the compositions of the present invention include central stimulant drugs. Central stimulant drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of amphetamine, methamphetamine, dextroamphetamine and methylphenidate.

Useful drug actives in the compositions of the present invention include antiarrhythmic drugs. Antiarrhythmic drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of propranolol, procainamide, disopyramide, quinidine, encainide, flecanaide, mexiletine and tocainide. Other antiarrhythmic drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of the quinidine derivatives disclosed in US-A-4,716,171 issued to Jarreau and Koenig on December 29, 1987. Highly preferred compounds included in this class include pharmaceutically-acceptable salts of 3S-hydroxy-10,11-dihydroquinidine, 3R-hydroxy-10,11-dihydroquinidine, 3R-hydroxy-O-acetyl-10,11-dihydroquinidine, and 3S-hydroxy-O-acetyl-10,11-dihydroquinidine, especially 3S-hydroxy-10,11-dihydroquinidine

Useful drug actives in the compositions of the present invention include β-adrenergic blocker drugs. β-Adrenergic blocker drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of metoprolol, acebutolol, betaxolol , labetalol and timolol. β-Adrenergic blocker drugs more preferred for inclusion in compositions of the present invention include metoprolol tartrate, acebutolol hydrochloride, betaxolol hydrochloride, labetalol hydrochloride and timolol maleate.

Useful drug actives in the compositions of the present invention include cardiotonic drugs. Cardiotonic drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of milrinone, amrinone and dobutamine. Other cardiotonic drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of 14-amino steroid derivatives, some of which are disclosed in US-A-4,325,879, US-A-4,552,868 and US-A-4,584,289, issued to Jarreau and Koenig on April 20, 1982, November 12, 1985 and April 22, 1986, respectively.

Useful drug actives in the compositions of the

present invention include antihypertensive drugs. Antihypertensive drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of enalapril, clonidine, hydralazine, minoxidil (which is also a hair growth stimulator drug), guanadrel, guanethidine, guanfacine, mecamylamine, methyldopate, pargyline, phenoxybenzamine and prazosin.

Useful drug actives in the compositions of the present invention include diuretic drugs. Diuretic drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of amiloride and hydrochlorothiazide. Diuretic drugs more preferred for inclusion in compositions of the present invention include amiloride hydrochloride.

Useful drug actives in the compositions of the present invention include vasodilator drugs. Vasodilator drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of diltazem, amiodarone, isoxsuprine, nylidrin, tolazoline and verapamil.

Useful drug actives in the compositions of the present invention include vasoconstrictor drugs. Vasoconstrictor drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of dihydroergotamine, ergotamine and methysergide.

Useful drug actives in the compositions of the present invention includes anti-ulcer drugs. Anti-ulcer drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of ranitidine and cimetidine.

Useful drug actives in the compositions of the present invention include include anesthetic drugs. Anesthetic drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of lidocaine, bupivacaine, chlorprocaine, dibucaine, etidocaine, mepivacaine, tetracaine, dyclonine, hexylcaine, procaine, cocaine, ketamine, pramoxine and phenol.

Useful drug actives in the compositions of the present invention include antidepressant drugs. Antidepressant drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of imipramine, desipramine, amitriptyline, nortriptyline, protriptyline, doxepin, maprotiline, phenelzine, tranylcypromine, trazodone and trimipramine.

Useful drug actives in the compositions of the present invention include tranquilizer and sedative drugs. Tranquilizer and sedative drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of chlordiazepoxide, benactyzine, benzquinamide, flurazepam, hydroxyzine, loxapine and promazine.

Useful drug actives in the compositions of the present invention include antipsychotic drugs. Antipsychotic drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of chlorprothixene, fluphenazine, haloperidol, molindone, thioridazine and trifluoperazine.

Useful drug actives in the compositions of the present invention include antimicrobial drugs (antibacterial, antifungal, antiprotozoal and antiviral drugs). Antimicrobial drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of β-lactam drugs, quinolone drugs, ciprofloxacin, norfloxacin, tetracycline, erythromycin, amikacin, triclosan, doxycycline, capreomycin, chlorhexidine, chlortetracycline, oxytetracycline, clindamycin, ethambutol, metronidazole, pentamidine, gentamicin, kanamycin, lineomycin, methacycline, methenamine, minocycline, neomycin, netilmicin, paromomycin, streptomycin, tobramycin, miconazole and amanfadine. Antimicrobial drugs preferred for inclusion in compositions of the present invention include tetracycline hydrochloride, erythromycin estolate, erythromycin stearate (salt), amikacin sulfate, doxycycline hydrochloride, capreomycin sulfate, chlorhexidine gluconate, chlorhexidine hydrochloride, chlortetracycline hydrochloride, oxytetracycline hydrochloride, clindamycin hydrochloride, ethambutol hydrochloride, metronidazole hydrochloride, pentamidine hydrochloride, gentamicin sulfate, kanamycin sulfate, lineomycin hydrochloride, methacycline hydrochloride, methenamine hippurate, methenamine mandelate, minocycline hydrochloride, neomycin sulfate, netilmicin sulfate, paromomycin sulfate, streptomycin sulfate, tobramycin sulfate, miconazole hydrochloride, amanfadine hydrochloride, amanfadine sulfate, triclosan, octopirox, parachlorometa xylenol, nystatin, tolnaftate and clotrimazole.

Useful drug actives in the compositions of the present invention include antineoplastic drugs. Antineoplastic drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of bleomycin, daunorubicin, doxorubicin, mechlorethamine, procarbazine, quinacrine, tamoxifen, vinblastine and vincristine.

Useful drug actives in the compositions of the present invention include antimalarial drugs. Antimalarial drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of chloroquine, hydroxychloroquine primaquine and quinine.

Useful drug actives in the compositions of the present invention include muscle relaxant drugs. Muscle relaxant drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of cinnamedrine, cyclobenzaprine, flavoxate, orphenadrine, papaverine, mebeverine, idaverine, ritodrine, dephenoxylate, dantrolene and azumolene.

Useful drug actives in the compositions of the present invention include antispasmodic drugs. Antispasmodic drugs preferred for inclusion in compositions

of the present invention include pharmaceutically-acceptable salts of the compounds disclosed in US-A-3,856,825 issued to Wright, Burch and Goldenburg on December 24, 1974.

Useful drug actives in th compositions of the present invention include antidiarrheal drugs. Antidiarrheal drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of loperamide.

Useful drug actives in the compositions of the present invention include bone-active drugs. Bone-active drugs preferred for inclusion in compositions of the present invention include pharmaceutically-acceptable salts of diphosphonate drug compounds and phosphonoalkylphosphinate drug compounds, including the prodrug esters thereof. Such compounds are disclosed, for example, in US-A-3,683,080 issued to Francis on August 8, 1972; US-A-4,304,734 issued to Jary, Rihakova & Zobacova on December 8, 1981; US-A-4,687,768 issued to Benedict & Johnson on August 18, 1987; US-A-4,711,880 issued to Stahl & Schmitz on December 8, 1987; and US-A-4,719,203 issued to Bosies & Gall on January 12, 1988; copending U.S. patent application Serial Nos. 808,584,* of Benedict & Perkins filed December 13, 1985; 945,069* of Ebetino, Buckingham & McOsker filed December 19, 1986; 945,068* of Ebetino & Benedict filed December 19, 1986; and 069,666* of Ebetino filed July 6, 1987; and EP-A-0,001,584 of Blum, Hempel & Worms, published May 2, 1979; EP-A-0,039,033 published April 11, 1981; EP-A-0,186,405 of Benedict & Perkins, published July 2, 1986; and EP-A-0,243,173 of Oku, Todo, Kasahara, Nakamura, Kayakiri & Hashimoto, published October 28, 1987.

Also useful in the present invention are sunless tanning agents including dihydroxyacetone, glyceraldehyde, indoles and their derivatives, and the like.These sunless tanning agents may also be used in combination with conventional sunscreen agents such as those disclosed in Segarin, et al., at Chapter VIII, pages 189 et seq., of Cosmetics Science and Technology, as well as wound healing agents such as peptide derivatives, yeast, panthenol, lamin and kinetin.

Other useful skin actives include skin bleaching (or lightening) agents including but not limited to hydroquinone, ascorbic acid, kojic acid and sodium metabisulfite.

Water-Soluble Polymer The polymers useful in the present invention are certain cationic polymers. These polymers are generally described in US-A-5,100,660, to Hawe et al., issued March 31, 1992; US-A-4,849,484, to Heard, issued July 18, 1989; US-A-4,835,206, to Farrar et al., issued May 30, 1989; US-A-4,628,078 to Glover et al. issued December 9, 1986; 4,599,379 to Flesher et al. issued July 8, 1986; and EP 228,868, to Farrar et al., published July 15, 1987.

The compositions of the instant invention comprise from 0.1% to 10%, preferably from 0.1% to 7.5%, and most preferably from 0.1% to 5% of the polymer.

In general these polymers are high molecular weight materials containing cationic, usually quaternized, nitrogen moieties. These polymers can be characterized by the general formula: $(A)_l(B)_m(C)_n$ wherein (A) is a dialkylaminoalkyl acrylate monomer or its quaternary ammonium or acid addition salt, (B) is a dialkylaminoalkyl methacrylate monomer or its quaternary ammonium or acid addition salt, (C) is a monomer having one carbon-carbon double bond, l is an integer of 0 or greater, m is an integer of 1 or greater, and n is an integer of 0 or greater. The (C) monomer can be selected from any of the commonly used monomers. Nonlimiting examples of these monomers include ethylene, propylene, butylene, isobutylene, eicosene, maelic anhydride, acrylamide, methacrylamide, maleic acid, acrolein, cycohexene, ethyl vinyl ether, and methyl vinyl ether. In the cationic polymers of the present invention, (C) is preferably acrylamide.

In highly preferred embodiments, these polymers also contain a crosslinking agent, which is most typically a material containing one or more unsaturated functional groups. Nonlimiting examples of suitable crosslinking agents include those selected from the group consisting of methylenebisacrylamides, diallyldialkyl ammonium halides, polyalkenyl polyethers of polyhydric alcohols, allyl acrylates, vinyloxyalkylacrylates, and polyfunctional vinylidenes. Specific examples of crosslinking agents useful herein include those selected from the group consisting of methylenebisacrylamide, ethylene glycol di-(meth)acrylate, di-(meth)acrylamide, cyanomethylacrylate, vinyloxyethylacrylate, vinyloxyethylmethacrylate, allyl pentaerythritol, trimethylolpropane diallylether, allyl sucrose, butadiene, isoprene, divinyl benzene, divinyl naphthalene, ethyl vinyl ether, methl vinyl ether, and allyl acrylate. Other crosslinkers include formaldehyde and glyoxal. Preferred for use herein as a cosslinking agent is methylenebisacrylamide.

When the croslinking agent is present, widely varying amounts can be employed depending upon the properties desired in the final polymer, e.g. viscosifying effect. Without being limited by theory, it is believed that incorporation of a crosslinking agent into these cationic polymers provides a material that is a more effective viscosifying agent without negatives such as stringiness and viscosity breakdown in the presence of electrolytes. The crosslinking agent, when present, can comprise from about 1 ppm to about 1000 ppm, preferably from about 5 ppm to about 750 ppm, more preferably from about 25 ppm to about 500 ppm, even more preferably from about 100 ppm to about 500 ppm, and most pref-

(*Equivalent Applications: USSN 808584 equivalent to US Patent 4,902,679; USSN 945069 equivalent to US Patent 4,868,164; USSN 945068 equivalent to European Patent 0,274,158; and USSN 0695666 equivalent to European Patent 0,298,553).

erably from about 250 ppm to about about 500 ppm of the total weight of the polymer on a weight/weight basis.

In one group of embodiments, these cationic polymers are made from processes which generally require polymerisation of a solution containing from about 20% to about 60%, generally from about 25% to about 40%, by weight monomer, in the presence of an initiator (usually redox or thermal) until the polymerization terminates. The temperature generally starts low, e.g. 0° to 95°C. The polymerization can be conducted by forming a reverse phase dispersion of an aqueous phase of the monomers into a nonaqueous liquid, e.g. mineral oil and the like.

When the polymer contains acrylamide, the molar proportion of acrylamide, based on the total molar amount of acrylamide, dialkylaminoalkyl acrylate and dialkylaminoalkyl methacrylate, is generally from about 20% to about 99%. Preferably, the amount of acrylamide is at least 50%, often at least 60% to below about 95%. All percentages describing the polymer herein are molar, unless otherwise specified.

Where monomer A is present, the ratio of monomer A:monomer B used in this process, and thus the ratio of groups A and B in the final polymer, on a molar basis is preferably about 80:20 to about 20:80. In one class of processes, the ratio is about 5:95 to 50:50, i.e., the cationic monomer is mainly methacrylate. In these processes, the ratio is generally being achieved in the range of from about 25:75 to about 5:95.

In another class of processes, the ratio A:B is from about 50:50 to about 85:15, the cationic monomers being mainly acrylate. Preferably the ratio A:B is about 60:40 to 85:15, most preferably about 75:25 to 85:15.

Preferred is where monomer A is not present and the ratio of monomer B:monomer C is from about 30:70 to about 70:30, preferably from about 40:60 to about 60:40 and most preferably from about 45:55 to about 55:45.

The polymerisation is preferably conducted under known conditions such that the polymers are water soluble and have a high molecular weight, generally about 1 million, for instance up to 30 million. The intrinsic viscosity, measured in molar sodium chloride solution at 25° C., is generally above 6, for instance from 8 to 14.

A cationic polymer useful herein is one conforming to the general structure $(A)_l(B)_m(C)_n$ wherein l is zero, B is methyl quaternized dimethylaminoethyl methacrylate, the ratio of B:C is about 45:55 to about 55:45, and the optional crosslinking agent is methylenebisacrylamide. This polymer which has the proposed CTFA designation, Polyquaternium 32 and Mineral Oil, is commercially available as Salcare SC92 from Allied Colloids Ltd. (Norfolk, VA).

Alternatively in another group of preferred embodiments, these cationic polymers do not contain the acrylamide monomer, that is, n is zero. In these polymers the (A) and (B) monomer components are as described above. An especially preferred group of these non-acrylamide containing polymers is one in which l is also zero. In this instance the polymer is essentially a homopolymer of a dialkylaminoalkyl methacrlyate monomer or its quaternary ammonium or acid addition salt. These diaklylaminoalkyl methacrylate copolymers and homopolymers preferably contain a crosslinking agent as described above.

A cationic homopolymer useful herein is one conforming to the general structure $(A)_l(B)_m(C)_n$ wherein l is zero, B is methyl quaternized dimethylaminoethyl methacrylate, n is zero, and the crosslinking agent is methylenebisacrylamide. This polymer, which does not as yet have a CTFA designation, will be referred to herein as crosslinked methyl quaternized dimethylaminoethyl methacrylate and mineral oil. This polymer is commercially available as Salcare SC95 from Allied Colloids Ltd. (Norfolk, VA).

Vehicle The compositions of the present invention are used along with pharmaceutically-acceptable carrier (or vehicle) components. The term "pharmaceutically-acceptable carrier components", as used herein, means compatible solid or liquid filler diluents which are suitable for administration to a human or lower animal. The term "compatible", as used herein, means that the components are capable of being commingled with the drug compounds, and other components of the compositions of the present invention, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the compositions of the present invention under ordinary use situations.

Pharmaceutically-acceptable carrier components must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the human or lower animal being treated.

Some examples of substances which can serve as pharmaceutically-acceptable carrier components are glycerol; ethanol; water; antioxidants; surfactants; chelating agents; preservatives; thickeners; anti-bacterial agents; as well as other non-toxic compatible substances used in pharmaceutical formulations.

These compositions can also contain one or more additional humectants/moisturizers, many of which may also be useful as actives. A variety of humectants/moisturizers can be employed and can be present at a level of from 0.5% to 30%, more preferably from 2% to 8%, and most preferably from 3% to 5%. These materials include polyhydroxy alcohols such as sorbitol, glycerin, hexanetriol, hexylene glycol and the like; sugars and starches; sugar and starch derivatives (e.g. alkoxylated glucose); D-panthenol and its derivatives; hyaluronic acid; lactamide monoethanolamine; acetamide monoethanolamine; and mixtures thereof.

Preferred humectants/moisturizers for use in the compositions of the present invention are the C_3-C_6 diols and triols. Especially preferred is the triol, glycerin.

The compositions of the present invention can also optionally compris at least one emollient. Examples of suitable emollients include, but are not limited to, volatile

and non-volatile silicone oils, highly branched hydrocarbons, and mixtures thereof. Emollients useful in the instant invention are further described in US-A-4,919,934, to Deckner et al., issued April 24 1990.

The emollients can typically comprise in total from about 1% to about 50%, preferably from about 1% to about 25%, and more preferably from about 1% to about 10% by weight of the compositions of the present invention.

The compositions of this invention may also contain pharmaceutically acceptable optional components that modify the physical and/or therapeutic effects of the compositions. Such optional components may include, for example, additional solvents, gelling agents, fragrances, preservatives, anti-bacterial agents, and stabilizers. However, such optional materials must not unduly interfere with the transdermal delivery of the drug active. Optional components useful in the compositions of this invention are described in the following patent documents: EP-A-0,043,738, Wickett et al., published January 13, 1982; and US-A-4,552,872, Cooper et al., issued November 12, 1985.

Most preferred compositions herein are gel-type compositions.

Another optional material is a solvent or co-solvent material. Such solvent materials include, for example, short chain alcohols and ethers. Preferred optional solvent materials include polyethylene glycols, dipropylene glycol, ethylene glycol monoethyl ether, ethanol, isopropanol, and dimethyl isosorbide. Water may also be used as a solvent or co-solvent in the compositions of this invention. If water is used in a saturated system, a gel or emulsion is preferably formed.

Most preferred compositions herein have a pH of below about 5, preferably below about 4, and most preferably below about 3. Without being limited by theory, the pH of a formulation can be an important factor in the delivery and availability of an active ingredient. For example, for the active ingredient salicylic acid, at pH values above its pK_a in a particular matrix, the salicylic acid would exist primarily in its ionized form and would not as readily penetrate into the skin. Thus, an acidic formulation range is preferred for salicylic acid compositions in order to supress ionization and enhance its penetration into the stratum corneum.

A wide variety of acids, bases, and buffers can be utilized to adjust and/or maintain the pH of the compositions useful in the instant invention. Materials useful for adjusting and/or maintaining the pH include sodium carbonate, sodium hydroxide, hydrochloric acid, phosphoric acid, sulfuric acid, acetic acid, sodium acetate, sodium hydrogen phosphate, sodium dihydrogen phosphate, citric acid, sodium citrate, sodium bicarbonate, triethanolamine, and the like.

Test Method

Transdermal penetration of drugs is conveniently determined and compared from various vehicles using the apparatus and procedure described below.

Full thickness excised human thigh skin is obtained from cadavers after all hair had been clipped and the skin washed. The skin samples are then bathed in 10% glycerin and stored frozen. The glycerin prevents the formation of ice crystals which could possibly damage the keratinized cells and/or the intercellular lipid matrix. After a rapid thawing, the skin is conditioned for 24 hours in Hank's Balanced Salt Solution with 1% antibacterial-antimycotic solution. Then the skin is washed with distilled water. A single skin donor is used for each experiment, and individual sections for use are selected based on integrity of the stratum corneum (visual determination). Selected areas are cut to $1cm^2$ using a scalpel.

Tests are conducted using glass diffusion cells placed in temperature-regulated stirring modules. Skin sections are mounted in the cells, and the receptor phase is added. The receptor phase is 50% Hank's Balance Salt Solution with 1% antibiotic-antimycotic solution. Each diffusion cell has an exposed area of $0.79cm^2$ and a receptor capacity of 5ml. Sufficient formulation is applied (750ul) to the surface of the skin to ensure infinite dose conditions, and the diffusion cell is covered with plastic wrap or parafilm to prevent product evaporation. At each sampling time the receptor phase is removed for analysis of drug content. The receptor phase is removed for analysis of drug content. The receptor phase is replenished at each sampling time in order to maintain sink conditions. Preferably 3 to 6 replicates are run with sampling intervals occurring at 1, 2, 4 & 6 hours.

Penetration rate (Flux) is determined as the quantity of drug penetrating a measured area of skin per hour during the 5 hour interval between 1 hour and 6 hours. Generally steady state is reached before 1 hour. Penetration rate is usually expressed as ug drug per cm^2 skin per hour.

Ingredients are identified by chemical or CTFA name.

EXAMPLES

Example I

An anti-acne composition is made by combining the following components using conventional mixing technology.

Ingredient	(%W/W)
Water, Purified	54.0
Alcohol SD 40	40.0
Polyquaternium-32 and Mineral Oil[1]	4.0
Salicylic Acid	2.0

[1]SalCare SC92 available from Allied Colloids, Suffolk, VA

Water is added to a suitable size container. While mixing at a moderate speed (300 rpm), the polyquaternium-32 and mineral oil is added to the water. Separately, the alcohol is placed in a container and covered. Using a Lightnin' Mixer with a 3 blade paddle prop, the salicylic acid is added to the alcohol and mixed at a low speed (100 rpm) until all salicylic acid is dissolved. The alcohol is slowly added to the water phase to form a gel. The resulting gel is mixed at moderate speed until uniform.

The compositions display skin penetration of the salicylic acid active as well as improved skin feel and residue characteristics together with excellent moisturizing, emolliency, rub-in and absorption characteristics.

Alternatively, the above composition is prepared by substituting the polyquaternium-32 and mineral oil with crosslinked methyl quaternized dimethylaminoethyl methacrylate and mineral oil, available as SalCare SC95 from Allied Colloids (Suffolk, VA).

Example II

An anti-acne and/or analgesic composition is made by combining the following ingredients utilizing conventional mixing techniques as described above in Example I.

Ingredient	(%W/W)
Water, Purified	55.0
Ibuprofen	2.0
Alcohol SDA 40	40.0
Polyquaternium-32 and Mineral Oil	4.0

The compositions display skin penetration of the Ibuprofen active as well as improved skin feel and residue characteristics together with excellent moisturizing, emolliency, rub-in and absorption characteristics.

Alternatively, the above composition is prepared by substituting the polyquaternium-32 and mineral oil with crosslinked methyl quaternized dimethylaminoethyl methacrylate and mineral oil, availabl as SalCare SC95 from Allied Colloids (Suffolk, VA).

Example III

A keratolytic composition for dermatological disorders is made by combining the following ingredients utilizing conventional mixing techniques as described above in Example I.

Ingredient	(%W/W)
Water	56.5
Urea	10.0
Benzyl Alcohol	0.5
Polyquaternium-32 and Mineral Oil	4.0

The compositions display skin penetration of the Urea active as well as improved skin feel and residue characteristics together with excellent moisturizing, emolliency, rub-in and absorption characteristics.

Alternatively, the above composition is prepared by substituting the polyquaternium-32 and mineral oil with crosslinked methyl quaternized dimethylaminoethyl methacrylate and mineral oil, available as SalCare SC95 from Allied Colloids (Suffolk, VA).

Example IV

A composition for sunless tanning is made by combining the following ingredients utilizing conventional mixing techniques as described above in Example I.

Ingredient	(%W/W)
Water	91.5
Benzyl Alcohol	0.5
Polyquaternium-32 and Mineral Oil	3.0
Dihydroxyacetyone	3.0
Glycerin	2.0

The compositions display improved skin penetration of the dihydroxyacetone as well as improved skin feel and residue characteristics together with excellent moisturizing, emolliency, rub-in and absorption characteristics.

Alternatively, the above composition is prepared by substituting the polyquaternium-32 and mineral oil with crosslinked methyl quaternized dimethylaminoethyl methacrylate and mineral oil, available as SalCare SC95 from Allied Colloids (Suffolk, VA).

Claims

1. A topical pharmaceutical composition having enhanced penetration through the skin characterized in that it comprises:

   (a) a safe and effective amount of a pharmaceutical active selected from anti-acne drugs, non-steroidal anti-inflammatory drugs, steroidal anti-inflammatory drugs, sunless tanning agents, sunscreen agents, wound healing agents, skin bleaching or lightening agents, antihistaminic drugs, antitussive drugs, antipruritic drugs, anticholinergic drugs, anti-emetic and antinauseant drugs, anorexic drugs, central stimulant drugs, antiarrhythmic drugs, β-adrenergic blocker drugs, cardiotonic drugs, antihypertensive drugs, diuretic drugs, vasodilator drugs, vasoconstrictor drugs, anti-ulcer drugs, anesthetic drugs, antidepressant drugs, tranquilizer and sedative drugs, antipsychotic drugs, antimicrobial drugs, antineoplastic drugs, antimalarial drugs, muscle relaxant drugs, antispamadic drugs, antidiarrheal drugs and bone-active drugs and mixtures thereof;
   (b) from 0.1% to 10.0% of a high molecular weight crosslinked cationic polymer of the formula: $(A)_l(B)_m(C)_n$ wherein (A) is a dialkylaminoalkyl acrylate monomer or its quaternary ammonium or acid addition salt, (B) is a dialkylaminoalkyl methacrylate monomer or its quaternary ammonium or acid addition salt, (C) is a monomer having one carbon-carbon double bond, l is an integer of 0 or greater, m is an integer of 1 or greater, and n is an integer of 0 or greater, wherein said polymer contains a crosslinking agent.

2. The composition of Claim 1 wherein the crosslinking agent is selected from the group consisting of methylene bisacrylamide, ethylene glycol di-(meth)acrylate, di-(meth)acrylamide, cyanomethylacrylate, vinyloxyethylacrylate, vinyloxyethylmethacrylate, allyl pentaerythritol, trimethylolpropane diallylether, allyl sucrose, butadiene, isoprene, divinyl benzene, divinyl naphthalene, ethyl vinyl ether, methyl vinyl ether, formaldehyde, glyoxal, allyl acrylate, and mixtures thereof.

3. A composition according to Claim 1 wherein (C) is acrylamide and wherein the crosslinking agent is methylenebisacrylamide.

4. The composition of Claim 3 wherein said pharmaceutical active is an anti-acne drug selected from salicylic acid, sulfur, resorcinol, N-acetylcysteine, octopirox, retinoic acid and its derivatives, benzoyl peroxide, erythromycin, zinc, tetracyclin, azelaic acid and its derivatives, phenoxy ethanol and phenoxy proponol, ethylacetate, clindamycin and meclocycline, flavinoids, lactic acid, glycolic acid, pyruvic acid, urea, scymnol sulfate and its derivatives, deoxycholate and cholate and mixtures thereof, preferably wherein said anti-acne drug is salicylic acid.

5. The composition of Claim 4 wherein the amount of (C) in the cationic polymer is from 50% to 90% molar.

6. The composition of Claim 4 wherein l in the cationic polymer is zero and the ratio of (B):(C) is from 45:55 to 55:45.

7. The composition of Claim 4 wherein both l and n are zero in the cationic polymer.

8. The composition of Claim 7 which further comprises from 3% to 5% glycerin.

9. The composition of Claim 3 wherein said antihistaminic drug is selected from chlorpheniramine maleate, chlorpheniramine tannate, triprolidine hydrochloride, triprolidine oxalate, diphenhydramine hydrochloride, diphenhydramine ascorbate, diphenhydramine citrate, doxylamine succinate, pyrilamine maleate, pyrilamine hydrochloride, pyrilamine tannate, phenindamine tartrate, promethazine hydrochloride, cyproheptadine hydrochloride, azatadine maleate, clemastine fumarate, carbinoxamine maleate, carbinoxamine hydrochloride, tripelennamine hydrochloride, tripelennamine citrate, dexchlorpheniramine maleate, brompheniramine maleate and chlorcyclizine hydrochloride and mixtures thereof; wherein said antitussive drug is selected from dextromethorphan hydrobromide, carbetapentane citrate, codeine phosphate and codeine N-oxide hydrochloride and mixtures thereof; wherein said anticholinergic drug is selected from scopolamine hydrobromide, scopolamine hydrochloride, atropine sulfate, atropine mucate, homatropine hydrobromide and homatropine hydrochloride and mixtures thereof; wherein said anti-emetic or antinauseant drug is selected from cyclizine hydrochloride, meclizine hydrochloride chlorpromazine hydrochloride and chlorpromazine maleate and mixtures thereof; wherein said anorexic drug is selected from benzphetamine hydrochloride, phentermine hydrochloride, chlorphentermine hydrochloride and fenfluramine hydrochloride and mixtures thereof; wherein said antimicrobial drug is selected from β-lactam drugs, quinolone drugs, ciprofloxacin, norfloxacin, tetracycline, erythromycin, amikacin, triclosan, doxycycline, capreomycin, chlorhexidine, chlortetracycline, oxytetracycline, clindamycin, ethambutol,

metronidazole, pentamidine, gentamicin, kanamycin, lineomycin, methacycline, methenamine, minocycline, neomycin, netilmicin, paromomycin, streptomycin, tobramycin, miconazole and amantadine, pharmaceutically-acceptable salts thereof and mixtures thereof; wherein said antiarrhythmic drug is selected from propranolol hydrochloride, procainamide hydrochloride, quinidine sulfate and quinidine gluconate and mixtures thereof; wherein said antihypertensive drug is selected from enalapril maleate, clonidine hydrochloride, hydralazine hydrochloride and hydralazine sulfate and mixtures thereof; wherein said anesthetic or antipruritic drug is selected from lidocaine hydrochloride, bupivacaine hydrochloride, chlorprocaine hydrochloride, dibucaine hydrochloride, etidocaine hydrochloride, mepivacaine hydrochloride, tetracaine hydrochloride, dyclonine hydrochloride and hexylcaine hydrochloride and mixtures thereof; wherein said bone-active drug is selected from 6-amino-1-hydroxy-hexanel,1-diphosphonic acid, 3-amino-1-hydroxy-propane-1,1-diphosphonic acid, octahydro-1-pyridine-6,6-diphosphonic acid, 2-(2'-piperidinyl)-ethane-1,1-diphosphonic acid, 2-(3'-piperidinyl)-ethane-1,1-diphosphonic acid, 2-(2'-piperidinyl)-1-hydroxy-ethane-1,1-diphosphonic acid, 2-(3'-piperidinyl)-1-hydroxy-ethane-1,1-diphos-phonic acid, N-(2'-(3'-methyl)-piperidinylidene)-amino- methane diphosphonic acid, N-(2'-(1',3'-diazinylidene))- aminomethane diphosphonic acid, and N-(2-(3-methyl-piperidinylidene))-aminomethanephosphonomethylphosphinic acid, or esters thereof and mixtures thereof; wherein said non-steroidal anti-inflammatory drug is selected from propionic acid derivatives, acetic acid derivatives, fenamic acid derivatives, biphenylcarboxylic acid derivatives, and oxicams and mixtures thereof, preferably wherein said non-steroidal anti-inflammatory drug is a propionic acid derivative selected from aspirin, acetaminophen, ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic acid, fluprofen and bucloxic acid and mixtures thereof; and wherein said sunless tanning agent is selected from dihydroxyacetone, indole derivatives and mixtures thereof.

10. The composition of claim 9 which further comprises a sunscreen active.

Patentansprüche

1. Topische pharmazeutische Zusammensetzung mit erhöhter Hautpenetration, dadurch gekennzeichnet, daß sie:

(a) eine sichere und wirksame Menge eines pharmazeutisch wirksamen Mittels, welches unter Arzneimitteln gegen Akne, nichtsteroidalen entzündungshemmenden Arzneimitteln, steroidalen entzündungshemmenden Arzneimitteln, Mitteln für das sonnenlose Bräunen, Sonnenschutsmitteln, Mitteln zur Heilung von Wunden, hautbleichenden oder -aufhellenden Mitteln, Antihistaminika, Antitussiva, Antipruriginosa, Anticholinergika, Antiemetika und Arzneimitteln gegen Übelkeit, Anorexika, das Zentralnervensystem stimulierenden Arzneimitteln, Antiarrythmika, adrenergen β-Blokkern, kardiotonischen Arzneimitteln, Antihypertensiva, Diuretika, gefäßerweiternden Arzneimitteln, gefäßverengenden Arzneimitteln, Arzneimitteln gegen Geschwüre, Anasthetika, Antidepressiva, Tranquillizern und Sedativa, Antipsychotika, antimikrobiellen Arzneimitteln, antineoplastischen Arzneimitteln, Arzneimitteln gegen Malaria, Muskelrelaxantien, Spasmolytika, Arzneimitteln gegen Diarrhö und knochenaktiven Arzneimitteln und Gemischen hievon ausgewählt ist;

(b) von 0,1 % bis 10,0 % von einem vernetzten kationischen Polymer mit hohem Molekulargewicht umfaßt, welches Polymer die Formel $(A)_l(B)_m(C)_n$ besitzt, worin (A) ein Dialkylaminoalkylacrylatmonomer oder dessen quaternäres Ammonium- oder Säureadditionssalz darstellt, (B) ein Dialkylaminoalkylmethacrylatmonomer oder dessen quaternäres Ammonium- oder Säureadditionssalz ist, (C) ein Monomer mit einer Kohlenstoff-Kohlenstoff-Doppelbindung darstellt, l eine ganze Zahl von 0 oder darüber ist, m eine ganze Zahl von 1 oder darüber ist und n eine ganze Zahl von 0 oder darüber ist, wobei das genannte Polymer ein Vernetzungsmittel enthält.

2. Zusammensetzung nach Anspruch 1, worin das Vernetzungsmittel von der Gruppe ausgewählt ist, welche aus Methylenbisacrylamid, Ethylenglycoldi(meth)acrylat, Di(meth)acrylamid, Cyanomethylacrylat, Vinyloxyethylacrylat, Vinyloxyethylmethacrylat, Allylpentaerythrit, Trimethylolpropandiallylether, Allylsaccharose, Butadien, Isopren, Divinylbenzol, Divinylnaphthalin, Ethylvinylether, Methylvinylether, Formaldehyd, Glyoxal, Allylacrylat und Gemischen hievon besteht.

3. Zusammensetzung nach Anspruch 1, worin (C) Acrylamid bedeutet und das Vernetzungsmittel Methylenbisacrylamid ist.

4. Zusammensetzung nach Anspruch 3, worin das genannte pharmazeutisch wirksame Mittel ein Arzneimittel gegen Akn ist, welches unter Salicyl-

säure, Schwefel, Resorcin, N-Acetylcystein, Octopirox, Retinoesäure und deren Derivaten, Benzoylperoxid, Erythromycin, Zink, Tetracyclin, Azelainsäure und deren Derivaten, Phenoxyethanol und Phenoxypropanol, Ethylacetat, Clindamycin und Meclocyclin, Flavinoiden, Milchsäure, Glycolsäure, Brenztraubensäure, Harnstoff, Scymnolsulfat und dessen Derivaten, Desoxycholat und Cholat und Gemischen hievon ausgewählt ist, worin das genannte Arzneimittel gegen Akne vorzugsweise Salicylsäure ist.

5. Zusammensetzung nach Anspruch 4, worin die Menge an (C) im kationischen Polymer 50 Mol-% bis 90 Mol-% beträgt.

6. Zusammensetzung nach Anspruch 4, worin I im kationischen Polymer 0 ist und das Verhältnis von (B):(C) von 45:55 bis 55:45 beträgt.

7. Zusammensetzung nach Anspruch 4, worin sowohl I als auch n im kationischen Polymer 0 sind.

8. Zusammensetzung nach Anspruch 7, welche ferner 3% bis 5% Glyzerin umfaßt.

9. Zusammensetzung nach Anspruch 3, worin das genannte Antihistaminikum unter- Chlorpheniraminmaleat, Chlorpheniramintannat, Triprolidinhydrochlorid, Triprolidinoxalat, Diphenhydraminhydrochlorid, Diphenhydraminascorbat, Diphenhydramincitrat, Doxylaminsuccinat, Pyrilaminmaleat, Pyrilaminhydrochlorid, Pyrilamintannat, Phenindamintartrat, Promethazinhydrochlorid, Cyproheptadinhydrochlorid, Azatadinmaleat, Clemastinfumarat, Carbinoxaminmaleat, Carbinoxaminhydrochlorid, Tripelennaminhydrochlorid, Tripelennamincitrat, Dexchlorpheniraminmaleat, Brompheniraminmaleat und Chlorcyclizinhydrochlorid und Gemischen hievon; worin das genannte Antitussivum unter Dextromethorphanhydrobromid, Carbetapentancitrat, Codeinphosphat und Codein-N-oxidhydrochlorid und Gemischen hievon ausgewählt ist; worin das genannte Anticholinergikum unter Scopolaminhydrobromid, Scopolaminhydrochlorid, Atropinsulfat, Atropinmucat, Homatropinhydrobromid und Homatropinhydrochlorid und Gemischen hievon ausgewählt ist; worin das genannte Antiemetikum oder das genannte Arzneimittel gegen Übelkeit unter Cyclizinhydrochlorid, Meclizinhydrochlorid, Chlorpromazinhydrochlorid und Chlorpromazinmaleat und Gemischen hievon ausgewählt ist; worin das genannte Anorexikum unter Benzphetaminhydrochlorid, Phenterminhydrochlorid, Chlorphenterminhydrochlorid und Fenfluraminhydrochlorid und Gemischen hievon ausgewählt ist; worin das genannte antimikrobielle Arzneimittel unter β-Lactam-Arzneimitteln, Chinolon-Arzneimitteln, Ciprofloxacin, Norfloxacin, Tetracyclin, Erythromycin, Amikacin, Triclosan, Doxycyclin, Capreomycin, Chlorhexidin, Chlortetracyclin, Oxytetracyclin, Clindamycin, Etahmbutol, Metronidazol, Pentamidin, Gentamycin, Kanamycin, Lineomycin, Methacyclin, Methenamin, Minocyclin, Neomycin, Netilmicin, Paromomycin, Streptomycin, Tobramycin, Miconazol und Amanfadin, pharmazeutisch annehmbaren Salzen hievon und Gemischen hievon ausgewählt ist; worin das genannte Antiarrhytmikum unter Propranololhydrochlorid, Procainamidhydrochlorid, Chinidinsulfat und Chinidingluconat und Gemischen hievon ausgewählt ist; worin das genannte Antihypertensivum unter Enalaprilmaleat, Clonidinhydrochlorid, Hydralazinhydrochlorid und Hydralazinsulfat und Gemischen hievon ausgewählt ist; worin das genannte Anästhetikum oder das genannte Antipruriginosum unter Lidocainhydrochlorid, Bupivacainhydrochlorid, Chlorprocainhydrochlorid, Dibucainhydrochlorid, Etidocainhydrochlorid, Mepivacainhydrochlorid, Tetracainhydrochlorid, Dycloninhydrochlorid und Hexylcainhydrochlorid und Gemischen hievon ausgewählt ist; worin das genannte knochenaktive Arzneimittel unter 6-Amino-1-hydroxy-hexan-1,1-diphosphonsäure, 3-Amino-1-hydroxy-propan-1,1-diphosphonsäure, Octahydro-1-pyridin-6,6-diphosphonsäure, 2-(2'-Piperidinyl)-ethan-1,1-diphosphonsäure, 2-(3'-Piperidinyl)-ethan-1,1-diphosphonsäure, 2-(2'-Piperidinyl)-1-hydroxy-ethan-1,1-diphosphonsäure, 2-(3'-Piperidinyl)-1-hydroxy-ethan-1,1-diphosphonsäure, N-(2'-(3'-Methyl)-piperidinyliden)-aminomethan-diphosphonsäure, N-(2'-(1',3'-Diazinyliden))-aminomethan-diphosphonsäure und N-(2-(3-Methyl-piperidinyliden))-aminomethanphosphonomethylphosphinsäure oder Estern hievon und Gemischen hievon ausgewählt ist; worin das genannte nichtsteroidale entzündungshemmende Arzneimittel unter Propionsäurederivaten, Essigsäurederivaten, Fenamsäurederivaten, Biphenylcarbonsäurederivaten und Oxicamen und Gemischen hievon ausgewählt ist, worin das genannte nichtsteroidale entzündungshemmende Arzneimittel vorzugsweise ein Propionsäurederivat ist, welches unter Aspirin, Acetaminophen, Ibuprofen, Naproxen, Benoxaprofen, Flurbiprofen, Fenoprofen, Fenbufen, Ketoprofen, Indoprofen, Pirprofen, Carprofen, Oxaprozin, Pranoprofen, Miroprofen, Tioxaprofen, Suprofen, Alminoprofen, Tiaprofensäure, Fluprofen, Bucloxinsäure und Gemischen hievon ausgewählt ist; und worin das genannte Mittel zum sonnenlosen Braunen unter Dihydroxyaceton, Indolderivaten und Gemischen hievon ausgewählt ist.

10. Zusammensetzung nach Anspruch 9, welche ferner ein Sonnenschutzmittel umfaßt.

Revendications

1. Composition pharmaceutique à usage local ayant une meilleure pénétration à travers la peau, caractérisée en ce qu'elle comprend:

   (a) une quantité sans danger et efficace d'une substance pharmaceutique active choisie parmi les médicaments antiacnéiques, les anti-inflammatoires non stéroïdiens, les anti-inflammatoires stéroïdiens, les agents autobronzants les écrans solaires, les agents de cicatrisation, les agents de blanchiment ou d'éclaircissement de la peau, les antihistaminiques, les antitussifs, les antiprurigineux, les anticholinergiques, les antiémétiques et les antinauséeux les anorexigènes, les médicaments stimulant au niveau central, les antiarythmiques, les bêtabloquants, les cardiotoniques, les antihypertenseurs, les diurétiques, les vasodilatateurs, les vasoconstricteurs, les anti-ulcéreux, les anesthésiques, les antidépresseurs, les tranquillisants et les sédatifs, les neuroleptiques, les antimicrobiens, les antinéoplasiques, les antipaludéens, les relaxants musculaires, les antispasmodiques, les antidiarrhéiques et les médicaments actifs sur l'os, et leurs mélanges;
   (b) de 0,1% à 10,0% d'un polymère cationique réticulé à haut poids moléculaire de formule: $(A)_l(B)_m(C)_n$ dans laquelle (A) est un monomère acrylate de dialkylaminoalkyle, son sel d'ammonium quaternaire ou son sel d'addition d'acide, (B) est un monomère méthacrylate de dialkylaminoalkyle, son sel d'ammonium quaternaire ou son sel d'addition d'acide, (C) est un monomère ayant une double liaison carbone-carbone, l est un nombre entier supérieur ou égal à 0, m est un nombre entier supérieur ou égal à 1, et n est un nombre entier supérieur ou égal à 0, dans laquelle ledit polymère contient un agent de réticulation.

2. Composition selon la revendication 1, dans laquelle l'agent de réticulation est choisi dans le groupe constitué par le méthylènebisacrylamide, le di-(méth)acrylate d'éthylèneglycol. le di(méth)acrylamide, le cyanoacrylate de méthyle, l'acrylate de vinyloxyéthyle, le méthacrylate de vinyloxyéthyle, l'allylpentaérythritol, l'éther diallylique de triméthylolpropane, l'allylsaccharose, le butadiène, l'isoprène, le divinylbenzène, le divinylnaphtalène, l'éthylvinyléther, le méthylvinyléther, le formaldéhyde, le glyoxal, l'acrylate d'allyle, et leurs mélanges.

3. Composition selon la revendication 1, dans laquelle (C) est l'acrylamide t dans laquelle, l'agent de réticulation est le méthylènebisacrylamide.

4. Composition selon la revendication 3, dans laquelle ladite substance pharmaceutique active est un médicament anti-acnéique choisi parmi l'acide salicylique, le soufre, le résorcinol, la N-acétylcystéine, l'octopirox, l'acide rétinoïque et ses dérivés, le peroxyde de benzoyle, l'érythromycine, le zinc, la tétracycline, l'acide azélaïque et ses dérivés, le phénoxyéthanol et le phénoxypropanol, l'acétate d'éthyle, la clindamycine et la méclocycline, les flavonoïdes, l'acide lactique, l'acide glycolique, l'acide pyruvique, l'urée, le sulfate de scymnol et ses dérivés, le désoxycholate et le cholate, et leurs mélanges, de préférence, dans laquelle ledit médicament anti-acnéïque est l'acide salicylique.

5. Composition selon la revendication 4, dans laquelle la quantité de (C) dans le polymère cationique est de 50% à 90% molaire.

6. Composition selon la revendication 4, dans laquelle l dans le polymère cationique est égal à zéro et le rapport de (B):(C) est de 45:55 à 55:45.

7. Composition selon la revendication 4, dans laquelle l et n sont tous deux égaux à zéro dans le polymère cationique.

8. Composition selon la revendication 7, qui comprend en outre de 3% à 5% de glycérine.

9. Composition selon la revendication 3, dans laquelle ledit antihistaminique est choisi parmi le maléate de chlorphéniramine, le tannate de chlorphéniramine, le chlorhydrate de triprolidine, l'oxalate de triprolidine, le chlorhydrate de diphénhydramine, l'ascorbate de diphénhydramine, le citrate de diphénhydramine, le succinate de doxylamine, le maléate de pyrilamine, le chlorhydrate de pyrilamine, le tannate de pyrilamine, le tartrate de phénindamine, le chlorhydrate de prométhazine, le chlorhydrate de cyproheptadine, le maléate d'azatadine, le fumarate de clémastine, le maléate de carbinoxamine, le chlorhydrate de carbinoxamine, le chlorhydrate de tripélennamine, le citrate de tripélennamine, le maléate de dexchlorphéniramine, le maléate de bromphéniramine et le chlorhydrate de chlorcyclizine, et leurs mélanges; dans laquelle ledit antitussif est choisi parmi le bromhydrate de dextrométhorphan, le citrate de pentoxyvérine, le phosphate de codéine et le chlorhydrate de N-oxyde de codéine, et leurs mélanges; dans laquelle ledit anticholinergique est choisi parmi le bromhydrate de scopolamine, le chlorhydrate de scopolamine, le sulfate d'atropine le muçate d'atropine, le bromhydrate d'homatropine et le chlorhydrate d'homatropine, et leurs mélanges; dans laquelle ledit antiémétique ou antinauséeux est choisi parmi le chlorhydrate de cyclizine, le chlorhydrat de

méclizine, le chlorhydate de chlorpromazine et le maléate de chlorpromazine, et leurs mélanges; dans laquelle ledit anorexigène est choisi parmi le chlorhydrate de benzphétamine, le chlorhydrate de phentermine, le chlorhydrate de chlorphentermine et le chlorhydrate de fenfluramine, et leurs mélanges; dans laquelle ledit antimicrobien est choisi parmi les médicaments à base de β-lactame, les médicaments à base de quinolone, la ciprofloxacine, la norfloxacine, la tétracycline, l'érythromycine, l'amikacine, le triclosan, la doxycycline, la capréomycine, la chlorhexidine, la chlortétracycline, l'oxytétracycline, la clindamycine, l'éthambutol, le métronidazole, la pentamidine, la gentamycine, la kanamycine, la lincomycine, la méthacycline, la méthénamine, la minocycline, la néomycine, la nétilmicine, la paromomycine la streptomycine, la tobramycine, le miconazole et l'amantadine, leurs sels pharmaceutiquement acceptables et leurs mélanges; dans laquelle ledit antiarythmique est choisi parmi le chlorhydrate de propranolol, le chlorhydrate de procaïnamide, le sulfate de quinidine et le gluconate de quinidine, et leurs mélanges; dans laquelle ledit antihypertenseur est choisi parmi le maléate d'énalapril, le chlorhydrate de clonidine, le chlorhydrate d'hydralazine et le sulfate d'hydralazine, et leurs mélanges: dans laquelle ledit anesthésique ou antiprurigineux est choisi parmi le chlorhydrate de lidocaïne, le chlorhydrate de bupivacaïne, le chlorhydrate de chlorprocaïne, le chlorhydrate de dibucaïne, le chlorhydrate d'étidocaïne, le chlorhydrate de mépivacaïne, le chlorhydrate de tétracaïne, le chlorhydrate de dyclonine et le chlorhydrate d'hexylcaïne, et leurs mélanges; dans laquelle ledit médicament actif sur l'os est choisi parmi l'acide 6-amino-1-hydroxyhexane-1,1-diphosphonique, l'acide 3-amino-1-hydroxypropane-1,1-diphosphonique, l'acide octahydro-1-pyridine-6,6-diphosphonique, l'acide 2-(2'-pipéridinyl)éthane-1,1-diphosphonique, l'acide 2-(3'-pipéridinyl)-éthane-1,1-diphosphonique, l'acide 2-(2'-pipéridinyl)-1-hydroxyéthane-1,1-diphosphonique, l'acide 2-(3'-pipéridinyl)-1-hydroxyéthane-1,1-diphosphonique, l'acide N-(2'-(3'-méthyl)pipéridinylidène)aminométhanediphosphonique, l'acide N-(2'-(1',3'-diazinylidène))aminométhanediphosphonique, et l'acide N-(2-(3-méthylpipéridinylidène))aminométhanephosphonométhylphosphinique, ou leurs esters et leurs mélanges; dans laquelle ledit anti-inflammatoire non stéroïdien est choisi parmi les dérivés d'acide propionique, les dérivés d'acide acétique, les dérivés d'acide fénamique, les dérivés d'acide biphénylcarboxylique et les oxicams, et leurs mélanges, de préférence, dans laquelle ledit anti-inflammatoire non stéroïdien est un dérivé d'acide propionique choisi parmi l'aspirin , l'acétaminophène, l'ibuprofène, le naproxène, le bénoxaprofène, le flurbiprofène, le fénoprofène, le fenbufène, le kétoprofène, l'indoprofène, le pirprofène, le carprofène, l'oxaprozine, le pranoprofène, le miroprofène, le tioxaprofène, le suprofène, l'alminoprofène, l'acide tiaprofénique, le fluprofène et l'acide bucloxique, et leurs mélanges; et dans laquelle ledit agent autobronzant est choisi parmi la dihydroxyacétone, les dérivés indoliques et leurs mélanges.

10. Composition selon la revendication 9, qui comprend en outre une substance active écran solaire.